REPLY BRIEF

Applicant	:	Paul P. Latta
App. No	:	10/823,263
Filed	:	April 13, 2004
For	:	A METHOD OF TREATMENT OF DIABETES THROUGH INDUCTION OF IMMUNOLOGICAL TOLERANCE
Examiner	:	Belyavskyi, Michail
Art Unit	:	1644

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Examiner's answer mailed November 16, 2006, Appellant submits this Reply Brief.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. The Examiner has rejected Claims 1-4, 6-11, 13 and 14 under 35 U.S.C. §103(a), as being obvious over USP 6,703,017, or by USP 5,425,764 or USP 5,629,194 each in view of Posselt et al. (*Ann. Surg.* 1991 **214**:363-373).

2. The Examiner has also rejected Claim 5 under 35 U.S.C. §103(a), as being obvious over USP 6,703,017, or by USP 5,425,764 or USP 5,629,194 each in view of Posselt et al. (*Ann. Surg.* 1991 **214**:363-373) as applied to claims 1-4 and 6-14, and further in view of USP 5,529,914.

ARGUMENT

1. The Examiner has improperly rejected Claims 1-4, 6-11, 13 and 14 as obvious over Posselt et al. In fact, Posselt et al. teaches away from the claimed invention.

In the Examiner's answer, the Examiner argued that the specific means of implanting a tolerizing dose recited in Claim 1 do not exclude implantation into the thymus. However, the claim specifically requires that the "implanting step is subcapsular, subcutaneous, intraperitoneal or intraportal." While the use of the term "comprising" does not exclude additional implantations, the claim requires that implantation occur into one of the recited sites. In other words, the cells must be implanted into the capsule of an organ (such as a kidney), under the skin, into the peritoneum, or into the portal vein leading into the liver.

As discussed in Appellant's brief, Posselt 1991 describes implanting unencapsulated islets into various areas of the body, including liver, kidney, and thymus, of spontaneously diabetic BB rats. The only implantation site that showed survival of the implanted cells was the thymus. The islets injected into the liver were rejected almost immediately, while islets injected into the kidney capsule had variable survival, with only two surviving as long as 120 days. In contrast, the intrathymic islet recipients were observed for a period close to the life span of the rat, without any recurrent diabetes. There is no indication of any kind in the Posselt 1991 reference that any site other than thymus can be used to induce immunological tolerance. Indeed, the authors state several times in this article that thymus is considered to be an immunologically privileged site.

In the experiments Posselt et al. conducted on intrathymically injected animals, approximately 100 days after the initial intrathymus transplantation, the transplanted rats were challenged with extrathymic allogeneic islets, which remained intact even after removal of the thymus bearing the islet allografts. However, in animals which were able to maintain functional subcapsular islets for more than 120 days, the vigor of the immune response to subsequent allografts was not diminished. As the authors stated several times in this article, thymus is considered to be an immunologically privileged site and is subject to the usual biologic characteristics of such sites, in that prior sensitization of the host with skin allografts precludes prolonged survival of intrathymic islets. The experiments, performed by Posselt et al. show just that, i.e. when allogeneic islets were transplanted into the thymus of recipients that had previously rejected donor strain skin grafts, the islets were destroyed in an accelerated manner,

demonstrating that the intrathymic site is readily accessible to activated T cells, and that no tolerance can be achieved using this protocol. Furthermore, Posselt et al. goes on to state that the achieved tolerization to intrathymic allografts is due to their direct influence on maturing thymocytes, which are more susceptible to tolerance-inducing signals, and that such "inappropriate" presentation of antigen by nonlymphoid cells induce a state of anergy in T cells.

If a skilled artisan was still looking for a way to solve the problem of creating tolerance to the implant other than described in the USP'017, USP'764, and USP'194, the publication of Posselt 1991 would point the artisan only in one direction: intrathymic implantation of a tolerizing dose of insulin-producing cells, because this reference convincingly teaches away from using tolerizing dose of insulin-producing cells anywhere but thymus, and it does not teach encapsulating these cells. Therefore, contrary to the Examiner's assertion, one skilled in the art would have no reasonable expectation of success in using the invention of the presently recited claims involving subcapsular, subcutaneous, intraperitoneal or intraportal implantation, and would have no motivation to do so after reading Posselt 1991.

Therefore, Posselt et al. clearly teaches away from using an initial dose of insulin-producing cells anywhere but thymus. Thus, the Posselt et al. reference clearly teaches away from implantation into the sites recited in Claim 1.

2. The Examiner has improperly rejected Claims 1 and 5 as being obvious over Posselt et al. in view of US Patent 6,703,017 or by US Patent 5,425,764, or US Patent 5,629,194, and further in view of USP 5,529,914. In the Examiner's answer, the Examiner included Claim 1 in this rejection for the first time. As discussed above, the Posselt et al. reference teaches away from implanting a tolerizing dose into any of the sites recited in Claim 1. The secondary references all relate to implantation of a curative dose. As such, none of the secondary references provide any teaching that would suggest implantation of a tolerizing dose into any of the recited sites. Thus, the combination of references fails to support a *prima facie* showing of obviousness with regard to Claim 1. In addition, Claim 5 includes all of the limitations of Claim 1. Therefore, Claims 1 and 5 are in compliance with 35 USC §103(a), and the rejection of Claims 1 and 5 as obvious should be withdrawn.

Conclusion

In view of the arguments presented, Appellants submit that Claims 1-14 are non-obvious over the cited references.

Respectfully submitted,

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CLAIMS APPENDIX

1. **(Previously presented)** A method of treating diabetes in a mammal in need thereof, comprising the steps of:

implanting in said mammal a tolerizing dose of insulin-secreting cells encapsulated in a biologically compatible permselective membrane, wherein said implanting step is subcapsular, subcutaneous, intraperitoneal or intraportal; then

administering to said mammal a therapeutic dose of corresponding unencapsulated insulin-secreting cells.

2. **(Original)** The method of claim 1, wherein said mammal is a human, canine or feline.

3. **(Previously presented)** The method of claim 1, wherein said tolerizing dose is one to two orders of magnitude less than said therapeutic dose.

4. **(Original)** The method of claim 1, wherein said insulin-secreting cells are pancreatic islet cells.

5. **(Original)** The method of claim 1, wherein said membrane comprises polyethylene glycol.

6. **(Previously presented)** The method of claim 1, wherein said tolerizing and therapeutic doses comprise porcine cells.

7. **(Previously presented)** The method of claim 1, further comprising the step of administering one or more anti-inflammatory agents to said mammal prior to, at the same time as, or subsequent to administration of said therapeutic dose.

8. **(Original)** The method of claim 1, wherein said membrane has a molecular weight cutoff of about 150 kDa or less.

9. **(Original)** The method of claim 1, wherein said membrane has a pore size of less than about 0.4 μm.

10. **(Original)** The method of Claim 9, wherein said membrane has a pore size of less than about 0.2 μm.

11. **(Previously presented)** The method of Claim 1, wherein said therapeutic dose is between one and two orders of magnitude higher than said tolerizing dose.

12. **(Cancelled)**

13. **(Original)** The method of Claim 1, wherein said administering step is intraperitoneal, intraportal or subcutaneous.

14. **(Original)** The method of Claim 1, wherein said tolerizing dose is administered incrementally.